REMARKS

Claims 6-18 are pending in the application. Claims 1-5 are cancelled without prejudice. Claims 6-18 are currently amended.

The Sequence Listing submitted with this response is made to correct a clerical error in which the open reading frame of SEQ ID NO. 4 was inadvertently offset in the last submission. This has required a corresponding revision of SEQ ID NOS. in the tables on pages 16-19 in the amendment to the Specification.

The Office objects to the recitation, as formerly recited in claim 12, of asparagines 45, 270 or 384 of Table 4. This positional reference was made to the translated amino acid sequence of the catalytic domain as shown in Fig. 1. and SEQ ID NO. 4. By way of illustration, the positional reference is adjusted for SEQ ID NO. 4 by adding 17 residues to the 45, 270 and 384 positions where the correct positional reference is now 62, 277 and 401, and these are the equivalent positions to what is now recited in claim 12. This amendment overcomes the objection.

The Office objects to FIGS. 1 and 4 as supplied with the last amendment because these were not labeled as "replacement sheets." The provision of replacement sheets 1/4 and 4/4 overcomes the objection. To unify the style, replacements sheets 2/4 and 3/4 are also being submitted for Figures 2 and 3.

The Office objects to the disclosure because the passage on page 5 at lines 19-21 refers to "the Not I site." Although this is not shown in Fig. 3, it is introduced as described on page 4 at lines 33-34. Therefore, use of "the" is proper. Accordingly, applicant respectfully traverses the objection and requests its withdrawal.

The Office objects to Figure 4 because it recites "proline nucleotides." The replacement sheet 4/4 now recites –proline residues—to overcome this objection as suggested by the Examiner.

The Office objects to claims 1-10 and 15-18 for the recitation of non-statutory subject matter and suggests that a word like "isolated" is required to show that the compositions are "made by the hand of man." A word like "isolated" is not required where, for example, SEQ ID NO. 3 was recited in claim 1 and on page 15 at line 18 has

underlining to show the part that is made by the hand of man; however, cancellation of claims 1-5 renders the objection moot with respect to these claims. Claim 6 has been amended to clarify that the "variant" cellobiohydrolase is "variant" with respect to the wild type, and so also is made by the hand of man. In like manner, each of claims 15-18 has underlining of the sequence as shown in Table 4 to show the part that is made by the hand of man. Therefore, Applicant traverses the rejection of claims 15-18 and has amended claim 6 to clarify the nature of "variant cellobiohydrolase" which means essentially that the sequence is made by the hand of man.

Claims 1-18 stand rejected under 35 U.S.C. §101 and §112, first paragraph, for failure to assert utility. Applicant respectfully disagrees and traverses these rejections. The problem addressed by Applicant was to provide genetic mutations that mitigate the problems that arise when *T. reesei* CBH1 is expressed in a heterologous host. The problem as discussed on page 1 at lines 25-33 is one of increasing the thermal tolerance of CBH1, which generally forces a reduction in saccharification temperatures because it is more heat labile than other members of a ternary reaction system in which CBH I may be used. Moreover, it is desirable to use other hosts, such as *A. awamori*, to overcome the well known problems of genetic engineering in *Trichoderma*. The Office has focused upon reduced glycosylation and the fact that Table 1 shows a quite small decline in activity with of reduced glycosylation in heterologously expressed CBH1; however, the comparison was at reduced temperature to accommodate the heat-labile unmutated enzyme. Accordingly, Table 1 does not bear upon the improved thermostability that is asserted on page 2 at lines 21-22. Other mechanisms for improved thermostability are generally the helix capping, strain removal, helix propensity, disulfide bridge mounts, deletion mutants, and proline replacement mutants taught in Example 5 and as shown in Tables 2-5. Therefore, the claims are supported by at least one specific utility and the Specification teaches many ways to accomplish this result. The utility requirement has never been that a composition must demonstrate enhanced utility. Applicant has demonstrated utility by showing in Table 1 that the mutations had their intended effect in *A awamori* of reducing glycosylation and retaining similar activity to that of wild type cDNA as expressed in *A.*

awamori. This could not have been predicted without undue experimentation at the time of the invention, especially in view of the Godbole et al. reference as applied by the Office. For these reasons, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C §101 and §112.

Claims 6-18 stand rejected for indefiniteness under 35 U.S.C §112, second paragraph. Various amendments to the claims have been made to overcome this rejection by addressing the specific issues raised by the Office. Claim 6 has been amended to delete the second "linker region." Claims 7-10 have been amended to depend from claim 6, as opposed to the cancelled claim 5. Claim 11 has been amended to clarify the manner of replacing the N-glycosylation site amino acid residue, and this has been done generally in the manner suggested by the Examiner. Claims 12-14 have been amended to change their dependancies to Claim 11 from that of Claim 10, and this resolves the issue of having method claims depending from Claim 10. Claim 12 has been further amended to clarify the nature of the N-glycosylation amino acid residues. Claim 13 has been amended to correct the spelling of "mutagenesis." Claims 15-17 have been amended to clarify that what is being claimed is a sequence change and to resolve the point of ambiguity raised by the Examiner. Claim 18 has been clarified by the addition of a Markush Group reciting a combination of the exoglucanases recited in claims 15, 16, and 7.

Claims 1-3 stand rejected under 35 U.S.C. §102(b) as being anticipated by the Nakari et al. references; however, the cancellation of claims 1-5 renders the rejection moot.

Claims 11-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Godbole et al. In formulating the rejection, the Examiner correctly presumed that claims 12-14 depend from claim 11. The reasoned basis for rejection is that Godbole noted the presence of glycosylation sites at Asp 45, 270 and 384, and also reported that overglycosylation was responsible for a diminution of activity in recombinant enzymes expressed in *P. pastoris*. But "obvious to try" is not the standard of obviousness, and the reference actually teaches away from doing what the Office now asserts is obvious. The Examiner must consider the reference in its entirety for what it does say, particularly in the first column on page 833:

> The molecular basis for partial or full inactivation as a result of overglycosylation, especially the reduction in action on cellulose, is not understood at this time. It is clear that these forms of rCBH I are not appropriate for structure-based enzyme engineering, however.

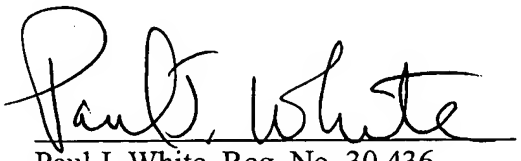
Those skilled in the art upon reading the above passage would conclude that there is no reason to try further experimentation because "these forms of rCBH I are not appropriate for structure-based enzyme engineering." This teaches away from precisely what is claimed, and a reference cannot be used in support of an obviousness rejection if it teaches away in this manner. Furthermore, the Examiner suggests it may have been "obvious to try" eliminating the glycosylation sites at positions 45, 270 and 384; however, the *reference* reports that "the mechanism is not understood at this time." Without the mechanism being understood, there is no clear teaching or suggestion for those skilled in the art to pursue what is presently claimed. This fact, particularly when combined with the instance of teaching away, makes a dispositive case for nonobviousness. Applicant's attorney respectfully solicits withdrawal of the rejection.

Claims 6 and 8 stand rejected under 35 U.S.C. §102(b) over Srisodsuk et al. The essential premise of the rejection rests on an erroneous presumption that "variant" can be given no patentable weight. Claim 6 has been amended to clarify that "variant" means with respect to the wild-type sequence, and so is not variant in context of evolution.

CONCLUSION

For the foregoing reasons, Applicants' attorney respectfully solicits a Notice of Allowance in this application. The Commissioner is authorized to charge any additionally required fees to Deposit Account No.14-0460. Should the Examiner have any questions, comments, or suggestions that would expedite the prosecution of the present case to allowance, Applicants' undersigned representative earnestly requests a telephone call at (303) 384-7575.

Respectfully Submitted,



Date: November 23, 2004.

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Amendments to the Drawings:

Please substitute the attached replacement sheets 1/4 through 4/4 for the corresponding sheets of figures in the application to replace figures 1 and 4 in the application as filed.